



Recent progress in tannic acid based approaches as a natural polyphenolic biomaterial for cancer therapy: A review

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ABSTRACT

Significant advancements have been noticed in cancer therapy for decades. Despite this, there are still many critical challenges ahead, including multidrug resistance, drug instability, and side effects. To overcome obstacles of these problems, various types of materials in biomedical research have been explored. Chief among them, the applications of natural compounds have grown rapidly due to their superb biological activities. Natural compounds, especially polyphenolic compounds, play a positive and great role in cancer therapy. Tannic acid (TA), one of the most famous polyphenols, has attracted widespread attention in the field of cancer treatment with unique structural, physicochemical, pharmaceutical, anticancer, antiviral, antioxidant and other strong biological features. This review concentrated on the basic structure along with the important role of TA in tuning oncological signal pathways firstly, and then focused on the use of TA in chemotherapy and preparation of delivery systems including nanoparticles and hydrogels for cancer therapy. Besides, the application of TA/Fe³⁺ complex coating in photothermal therapy, chemodynamic therapy, combined therapy and theranostics is discussed.

1. Introduction

One of the most impactful diseases is cancer, which affects populations of diverse ethnic, social, and economic characteristics. It has yet been represented as the second cause of death worldwide after cardiovascular disease, although many conventional therapies have been applied, including surgery, chemotherapy, and radiation therapy [1–5]. These strategies, despite significant advancements, fail or fall short of their potential because of certain shortcomings such as multidrug resistance, instability, low solubility, low distribution, and non-specificity [6–8]. Because of the wide application of tannic acid (TA) in delivery systems, diagnosis, and imaging, there is a growing interest in the implementation of TA based delivery systems for cancer treatment. Various nanomaterials have been utilized for cancer therapy, including liposomes, bioceramics, polymers, micelles, carbon nanotubes, mesoporous silica, etc. [9–17]. Among them, natural-based nanomaterials and biomaterials are used for different cancer therapy

by inhibiting cancer cell growth and arresting metastasis due to their inexpensive, facile available, nontoxic, and safe nature [17,18]. Accordingly, the development of phenolic natural compounds and other plant materials has been of great interest in cancer therapy due to their unique features.

TA is a plant polyphenol [19,20] found in various sources including plants, fruits, teas, nuts, and coffee grains [21–23]. With a hydrophobic “core” and hydrophilic “shell”, TA can adhere to different sorts of material and interact with hydrophilic and hydrophobic ones such as particle and planar ones, etc. Due to multibonding sites, TA can improve the solubility of hydrophobic substrates via various interactions. The critical features of TA are nontoxic nature, stable compound, biocompatibility, antioxidant [24–26], antimutagenic, antimicrobial [27,28], homeostatic [29], neuroprotective [30], anti-inflammatory and astringent [31]. TA demonstrated anticancer potential against different cancer cell lines [32] including liver HepG2 [33] and glioma HS 683 [34]. Therefore, TA has been highly desirable for biomedical applications,

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including nanomedicine, cancer therapy and diagnostics. This review focused on the properties of TA along with its fundamental nature in anticancer activity, as well as providing the positive roles of TA in chemotherapy (sensitizing cancer cells and decreasing the toxicity of chemotherapy drugs). Moreover, the use of TA in delivery systems including nanoparticles and hydrogels for cancer therapy is discussed along with the potential of TA/Fe³⁺ complex coated nanoparticles in the fields of photothermal therapy (PTT), chemo dynamic therapy (CDT) and theranostics.

1.1. Structure and properties of TA

The different behavior of TA, a class of polyphenolic compounds, is closely related to the molecular structure. Thus, it is necessary to have a good understanding of the structure of TA. TA was recognized early on as the most famous tanning material. It has a structure consisting of decagalloyl groups surrounding glucose (core) by ester linkages (Fig. 1a) with the empirical formula of C₇₆H₅₂O₄₆ after analyzing the structure of the TA by Adolf Strecker, K. Feist and Emil Fisher [20,22,35–38]. The presence of some functional groups (including phenolic hydroxyl groups, estric groups, and aromatic rings) in TA makes it an excellent candidate for noncovalent, such as dipole-dipole, electrostatic,

coordination, etc. and/or covalent interactions with biological systems [39]. Because of the multiplicity of phenolic hydroxyls, TA is extremely soluble in water [40] but has a weak acidity with a pK_a ranging from 2.5 to 8.5 [41–43]. The hydroxyl groups can act as both hydrogen bond (HB) donor and hydrogen bond acceptor [44]. The presence of aromatic rings can also enable it to interact with other molecules via hydrophobic or π -stack interactions [45]. Besides, there is a coordination interaction between metal ions (Mⁿ⁺; Co²⁺, Fe³⁺, Cu²⁺, etc.) and the lone pairs of the hydroxyl group, leading to TA/metal complexes [37,43,46,47]. Compared to HB, coordination has particularly strong interactions [48]. Therefore, the coordination interactions can play an important role in molecular interactions of relevance to biological systems. For example, the interaction of hydroxyl groups of TA with protein and other macromolecules leads to strong complexes. The TA/Mⁿ⁺ complexes structure is strongly dependent on certain environmental conditions. The findings showed that TA/Fe³⁺ complexes can be performed through three kinds of mono-, bis-, and tris-complex interactions under different pH conditions because of protonation/deprotonation of phenolic hydroxyl groups (Fig. 1b) [37,49,50]. So that, in an acidic environment, more phenolic hydroxyl groups are protonated and consequently, O...Fe coordination interactions decrease. Also, Guo and coworker demonstrated that the ionic strength can affect the structure [49,51–53]. In the

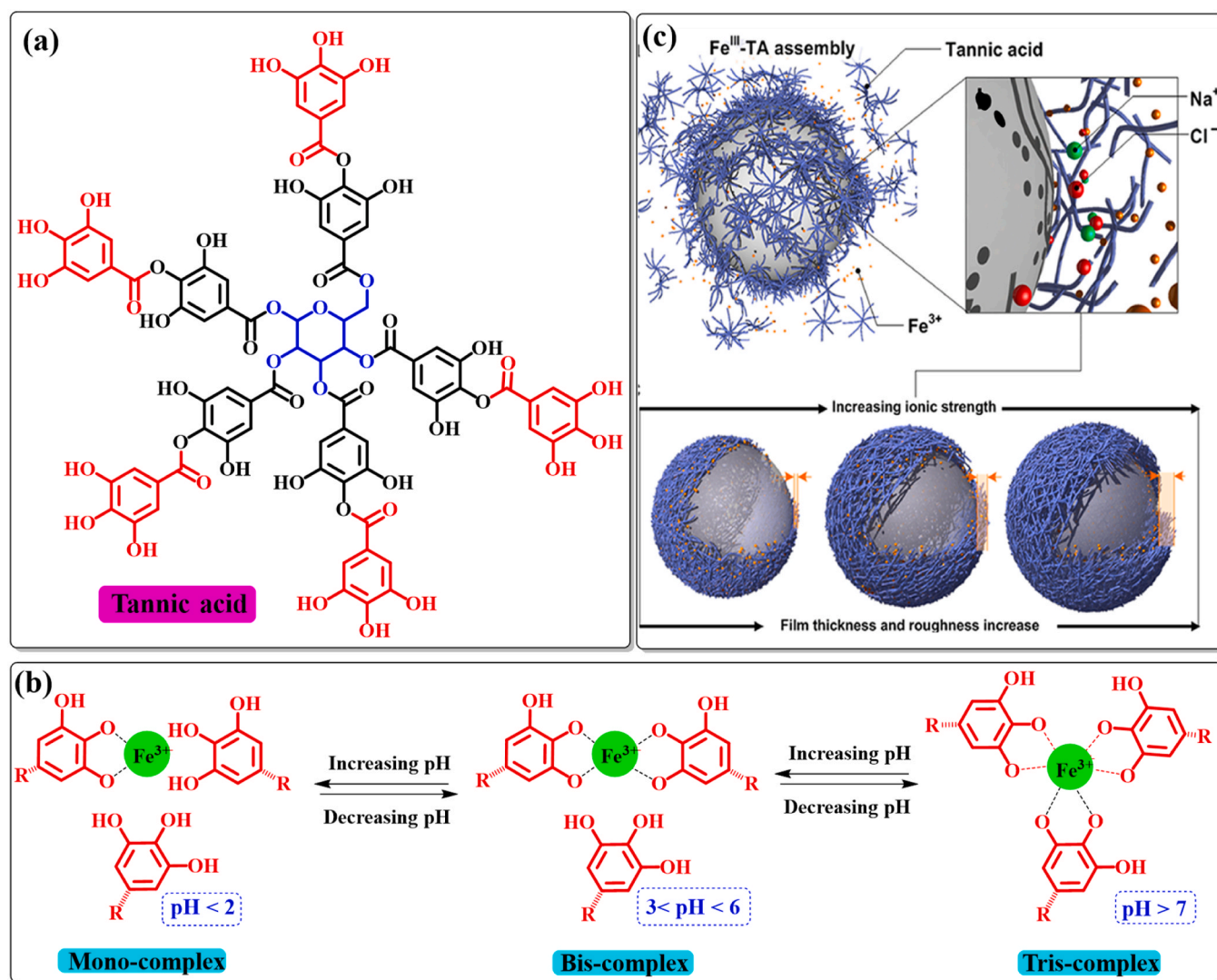


Fig. 1. Tannic acid (TA); (a) structure, (b) different Fe³⁺/TA complex formation (controlled by pH). (c) different configuration of complex (controlled by ionic strength).

(a-b) Reprinted with permission of ref [53], (c) Reprinted with permission of ref [52].

presence of a positive charge, the configuration of TA is extended due to high ionic strength (Fig. 1c) [52].

TA, as an anticancer agent, has been well recognized in the field of medicine as well as pharmaceutical and biological applications. TA has been utilized with numerous benefits for different applications, such as the preparation of different carriers including nanoparticles and hydrogels for delivery of anticancer drugs. The properties and applications of TA are discussed below:

1.2. The anticancer mechanisms of TA

A wide variety of natural compounds have shown promising results in the prevention, treatment and/or inhibition of cancer. The multistep process of carcinogenesis includes a sequences of transition states that begin with initiation, promotion, and progression and ending with

metastasis to other organs [54,55]. Ahmed and coworker indicated that natural compounds can halt carcinogenesis via various molecular mechanism including cell apoptosis, regulation of cell cycle, invasion, migration, and other signaling pathways [56]. As a natural compound, TA plays an important role in each transition step in the process of carcinogenesis [57]. Cell cycle arrest, induction of apoptosis, reduction of cell proliferation and migration, and adhesion of several cancer cell lines have been observed for TA. The main mechanism involves modulation of signaling pathways such as EGFR/Jak2/STATs, TGF- β , and NF- κ B or inhibition of PKM2 glycolytic enzyme. Rana et al. [58] reported high anticancer activities of TA against numerous solid malignancies, including lung, breast, ovarian, and colorectal cancer. It was found that several oncological signal pathways such as VEGF/VEGFR, RAS/RAF/mTOR, JAK/STAT, TGF- β 1R /TGF- β 1R axis and CXCL12/CXCCR4 axes were also directly influenced by TA. For example,

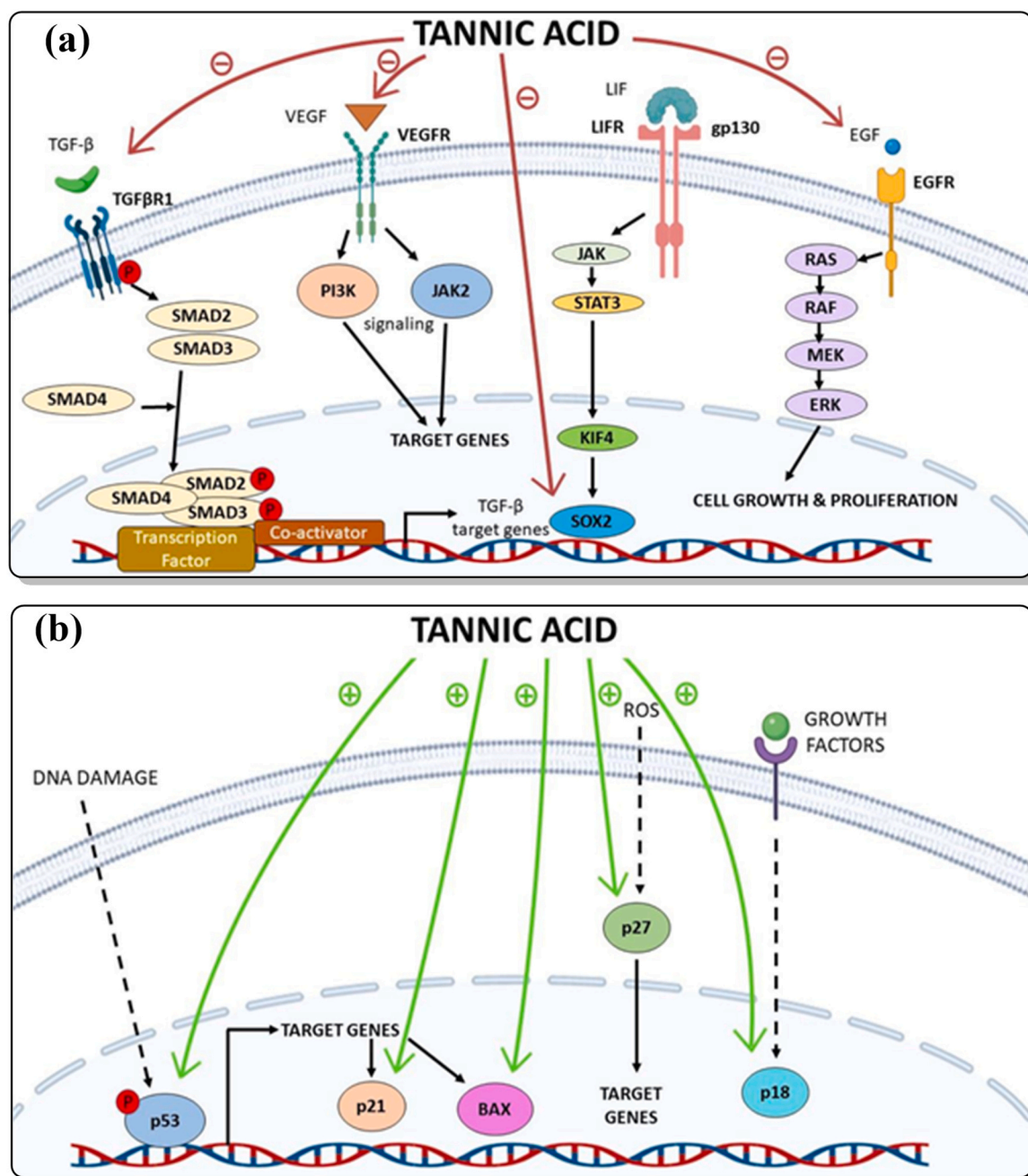


Fig. 2. a) Repress of multiple essential protein via TA in several oncological signaling pathways. b) significant induction effects on tumor suppressor protein by TA. (a) Reprinted with permission of ref [58], (b) Reprinted with permission of ref [58].

Darvin and coworkers indicated that TA has the ability to regulate both the canonical EGF-R/Jak2/STAT pathway and the non-canonical p38/STAT1 pathway. TA utilizes the non-canonical p38/STAT1/p21-Waf1/Cip1 signaling axis with STAT1 ser727 as the critical factor to induce G1 arrest. Additionally, for the induction of apoptosis, TA employs the canonical EGF-R/Jak2/STAT3/Bcl-2 signaling axis. These results highlight the role of TA in gene-specific regulation, G1 arrest, and apoptosis induction. [59]. The molecular mechanism of anticancer activities (intracellular target protein) by TA for some cancers exhibited in Fig. 2a and b, this is carried out by inhibiting VEGF/VEGFR, transcription of the TGF- β as well as angiogenesis signaling pathway in cancer. Additionally, TA has the ability to inhibit the EGF/EGFR signaling pathway, suppress SOX2 gene expression, and impede proliferation. As shown in Fig. 2b, TA enhances the phosphorylation of p53, resulting in increased expression of its target genes, including p21 and BAX. Furthermore, TA can stimulate the expression of p21, BAX, p27, and p18.

Furthermore, TA can induce endoplasmic reticulum (ER) stress through the unfolded protein response (UPR) pathway and subsequently promote apoptosis for cancer therapy. ER stress can reduce cell survival and enhance the apoptosis of cancer cells. ER, as a cell organelle, performs various functions including synthesis, maturation, folding, and transfer of proteins.

The accumulation of unfolded proteins caused by ER stress can be destroyed through proteolytic mechanisms including ubiquitination/proteasome and autophagy [60,61]. In the ER membrane, there are three stress sensors including activating transcription factor 6 (ATF6), inositol-requiring protein-1 α (IRE1), and protein kinase RNA-like endoplasmic kinase (PERK). As a glucose-regulated protein (GRP78), binding immunoglobulin (BiP) is a main regulator of ER function responsible for UPR induction and cancer cell survival [62]. TA induces apoptosis and arrest the cell cycle by inducing ER stress. Stress dissociates BiP from these three ER sensors and causes oligomerization, trans-phosphorylation, and activation of these sensors [63].

Moreover, TA affects cell survival by effectively regulating lipid metabolism and disrupting cell membranes as well as nuclear membranes. Nagesh et al. investigated the lipid targeting ability of TA and its ability to induce ER stress by ROS in prostate cancer cells. Prostate cancer cells use the aberrant lipid signaling and metabolism as a survival advantage. Also, the storage of intracellular lipid serves as a fuel for the proliferation of prostate cancer cells. It was found that TA shifts the balance of cell survival towards apoptosis by inhibiting lipogenic signaling and suppressing lipid metabolic pathways [32].

1.3. The positive roles of TA in chemotherapy

Chemotherapy is the most effective treatments for cancer. Inhibition of some pathways such as proliferation signal pathways leads to apoptosis of tumor cells [64–66]. The main limitations of chemotherapeutics are drug resistance mechanisms and nonspecific toxicity towards normal cells [67,68]. Various natural compounds with excellent properties and novel functions, including TA, has been applied for cancer treatment via various approaches [69,70] including as chemotherapeutic agents [71,72], chemopreventive agents [73] and chemosensitizing agents [74]. Overall, TA has great potential application in chemosensitizing to overcome multidrug resistance and reduce chemotherapy toxicity.

1.4. Sensitization of cancer cell to chemotherapy

One of the main obstacles of chemotherapy is multidrug resistance (MDR) in cancer cells, which can increase the likelihood of mortality. The superfamily members of ATP-binding cassette (ABC) transporters are well-known as major cause of MDR. The ABC transporters are ubiquitous membrane proteins that contain at least 49 genes in humans and are present in all prokaryotes, fungi, plants, yeast and animals.

Among the ABC transporter family, three ABC transporters including P-glycoprotein (P-gp), multidrug resistant protein 1 (MRP1) and breast cancer resistance protein (BCRP) are the most important drug transporters reported in human cancer [75–77]. P-gp is the crucial target of potential chemosensitizers expressed in different cancers [68,78,79].

ABC transporters, as an example of ATP-dependent pumps, not only efflux drugs, but also carry endogenous substances such as peptides, amino acids, lipids and inflammatory mediators. Overexpression of ABC transporters has been well recognized as the major mechanism involved in conferring MDR, which can increase the efflux of chemotherapeutic drugs from cancer cells and thereby diminish the intracellular drug concentration. Inhibition of ABC transporters is a recent strategy aimed at overcoming MDR in cancer chemotherapy. As a plant polyphenol, TA can be used to overcome MDR for chemotherapy purposes by reducing the activity of P-gp, MRP1 and MRP2 efflux pumps and inhibiting cellular efflux pathways. Therefore, TA can improve the effectiveness of chemotherapy drugs and overcome drug resistance by modulating the pathways of drug efflux [80]. The results show that TA has a positive role in the chemosensitization effect [81].

As a second point, the inhibition of the proteasome activity by TA is another reason to overcome drug resistance, thereby allowing it to use on chemotherapy. This proteolytic enzyme, proteasome, causes intracellular protein degradation, which leads to tumor growth and drug resistance. Therefore, one of the most important and effective mechanisms to overcome drug resistance and sensitize cancer cells to chemotherapy is proteasome inhibition [82]. Proteasome inhibition by TA on 20 S and 26 S proteasome was performed in various cell types and tumor-bearing mouse models [68,83]. Inhibition of proteasome leads to increased expression of p27 and Bax as well as impaired cell cycle progression [84].

With some limitations such as, low bioavailability, low lipid solubility, short half-life, combination of TA with conventional chemotherapy agents such as doxorubicin (DOX), paclitaxel, and cisplatin is desirable in different cancers such as breast, ovarian, and pancreatic cancer without affecting normal human epithelial cells. Hence, the combination of TA and anticancer drugs can potentially bring extraordinary anti-cancer outcomes. For example, combining TA with DOX can sensitize cancer cells to chemotherapy, which is applied for colon cancer cell line (Caco-2) and lymphoblastic leukemia cell line (CEM/ADR 5000) [78].

1.5. Decreasing toxicity of chemotherapy drugs

Despite the significant advancement in the treatment of cancer with most effective drugs, some of them have negative effects (symptoms of direct toxicity) on different parts of the body, causing annoying symptoms and severely debilitating patients. It is necessary to use appropriate methods and materials to reduce the toxicity associated with anticancer treatment and chemotherapy. Different techniques are used to overcome this problem, for example, cytoprotective agents offer opportunities to reduce the treatment-related toxicity of anticancer therapy and perhaps increase the dose and dose intensity of radiation and chemotherapy [85]. Chemotherapy drugs that can cause irreversible toxicity include anthracyclines; alkylating agents; taxanes; topoisomerase inhibitors. DOX is one of the chemotherapeutic drugs (anthracyclines) for various types of cancer, which has hampered its applications due to cardiotoxicity [86]. Different mechanisms, including oxidative stress, apoptosis and inflammation induce cardiotoxicity in which oxidative stress plays a crucial role among them [87,88]. Generated oxidative stress by DOX can induce inflammatory response by stimulating redox-sensitive transcription factors [89]. One of the methods to deal with these problems is to use natural compounds. These compounds, especially TA, can neutralize the toxic effect of DOX without reducing the antitumor activity of drug. Studies have shown that treatment with TA efficiently ameliorates DOX-induced cardiotoxicity [89,90]. Jianping Zhang reported that TA can considerably inhibit cardiotoxicity by inhibiting

oxidative stress, inflammation and apoptotic damage, thereby decreasing toxicity of chemotherapy [90].

2. Utilization of TA in delivery systems for cancer therapy

TA with multibinding sites can crosslink with various macromolecules through noncovalent interactions including hydrogen bonding, electrostatic and hydrophobic. Thus, TA has been utilized in various studies for preparation of TA crosslinked hydrogel and nanoparticles [42,91,92]. TA as HB donor can interact with synthetic and natural polymers to form multilayer films, microcapsules or microparticles by hydrogen bonding [42,93–95]. Table 1 demonstrates some TA based nanoparticles systems for cancer therapy application.

Table 1
nanoparticles systems based on tannic acid (TA) for cancer treatment.

Platform	base	mechanism of action	characteristics	Ref
TA/Fe ³⁺ modified poly (lactic-co-glycolic acid) (DOX-TPLGA NPs)	polymeric nanoparticle	tumor-targeted delivery of doxorubicin	-enhanced drug uptake and superior cytotoxicity of breast cancer cells -enhance the safety and efficacy of chemotherapy drugs	[108]
TA/Fe ³⁺ complex coated on mesoporous silica (DOX@MSN-pTA)	polymeric nanoparticle	combined chemo-photothermal therapy, delivery of doxorubicin	-enhanced cytotoxicity against the 4T1 tumor cells -enhanced anti-tumor efficacy	[148]
encapsulation of CaO ₂ with ZIF-8 and assembled Fe ³⁺ /TA on the surface (CaO ₂ @ZIF8 @MPN)	Hybrid (organic-inorganic) nanoparticles	chemodynamic therapy	-enhanced CDT synergistic antitumor ion therapy -improved the efficiency of Fenton reaction	[180]
AuNP-TA	metal nanoparticle	targeted therapy, ROS-dependent mitochondrial apoptosis	inducing apoptotic cell death of HCT116 cells via the ROS/P53/Akt axis	[213]
keratin-TA (KNPs)	polymeric nanoparticle	targeted therapy, pH/GSH dual responsive drug carriers for doxorubicin	the ability for therapeutic delivery, TME triggered drug release.	[120]
TA-AgNPs	metal nanoparticle	the ability for delivery of anticancer agent (epirubicin hydrochloride)	good tumor suppression, good ability to load and deliver anticancer drug, pH- and GSH-sensitive drug release	[214]
TA/ Fe ³⁺ /BNS	inorganic nanoparticles	MRI theranostics	increase in apoptotic cells by decreasing in cell proliferation, tumor targeting ability	[197]

2.1. Preparation of nanoparticles using TA

Carriers based on nanotechnology enhance the therapeutic efficiency of anticancer drugs by improving some properties including solubility, bioavailability, and retention time in tumor site, as well as the ability to target tumors. Several studies have demonstrated the effective transfection of many drugs into tumor tissues using various nanoparticles [96–98]. Different procedures have been applied for the synthesis of metal nanoparticles, including chemical, physical (chemical reduction, ion sputtering, laser ablation, sol-gel, solvothermal) and green technique (biological) [99,100]. Among a wide range of reducing agents (to reduce Mⁿ⁺ to M⁰) [101,102], TA has been widely used for the synthesis of different nanoparticles [103–105]. In the redox reaction, the phenolic groups of TA were oxidized and converted to quinone structure, thereby acting as electron donor. The released electrons naturally lead to the reduction of Mⁿ⁺ ion to form corresponding metal nanoparticles (Fig. 3a). By using TA as a coreductant, bimetallics have also been reduced to nanoparticles [106,107]. The morphologies of nanoparticles are controlled by several factors such as temperature, pH, and molar ratio (Fig. 3b).

The interaction of TA with therapeutic agents (complexation or self-assembly) has been broadly used in drug delivery systems [96–98]. Sumeet S. Chauhan et al. encapsulated some anticancer drugs (including gemcitabine, 5-fluorouracil and irinotecan) with TA-pectin, which treated pancreatic cancer adenocarcinoma cell lines upon nanocomplexes formation [108,109]. TA can improve the therapeutic efficacy of nanoparticles through the inhibitory function of P-gp by ATPase [110]. Kitagawa et al. have indicated that P-gp inhibition is carried out by hydrogen bonding interactions between galloyl moieties of TA with the P-gp regulatory region [111]. Oral chemotherapy is of great interest because of its low costs, high safety and high patient compliance [112, 113], but some anticancer drugs are sensitive in the hostile gastrointestinal environment and usually exhibit low permeability across the intestinal epithelium [114–116]. Therefore, it is highly desirable to overcome multiple biological barriers in the gastrointestinal tract, including acidic/enzymatic degradation of the intestinal epithelium [113,117]. In a study by Zicheng Li to achieve this goal, paclitaxel (PTX) was loaded into TA/poly(N-vinylpyrrolidone) nanoparticles (PTX-NP).

The presence of TA, in addition to P-gp inhibitory function, leads to improved trans-epithelial transport properties, and prolonged intestinal retention for the nanoparticle system. Hollow polymeric particles can be prepared through layer-by-layer technique, which can provide high loading and controlled release of drugs to decrease their toxicity and increase their efficacy. Owing to hydrogen bond interactions, the TA based multilayer assembly is an attractive capsule for encapsulating anticancer drugs. Using the TA-poly(N-vinylpyrrolidone) multilayers, Fei Liu and coworkers encapsulated DOX with high efficiency under different condition (ionized and neutral forms of TA and low and high salt polymer solution) [39].

The development of smart drug carriers, which leads to drug release in specific tumor microenvironments (TME), including pH, hypoxic condition and abnormal levels of ROS is highly desirable [118]. TME is another factor that contributes to the failure of conventional drug delivery strategies to kill cancer cells [119]. It is known as a main factor in cancer progression and drug resistance. The TME promotes the function of tumor cells by regulating their basic survival. Interaction between structural constituents and TME leads to aggressiveness and metastatic spread of cancer cells to distant locations. TME is formed after the colonization of tumor cells in normal tissues and the change of the surrounding microenvironment through the recruitment of cancer-associated fibroblasts, the regulation of immune cells and the regulation of their secreted factors, and the formation of neo-vascularization by vascular endothelial cells. The development of TA-based drug delivery has been expanded to a wide range of applications to address this limitation. In some studies, TA has been used to prepare smart nanoparticles to deliver anticancer drugs. Hydroxyl

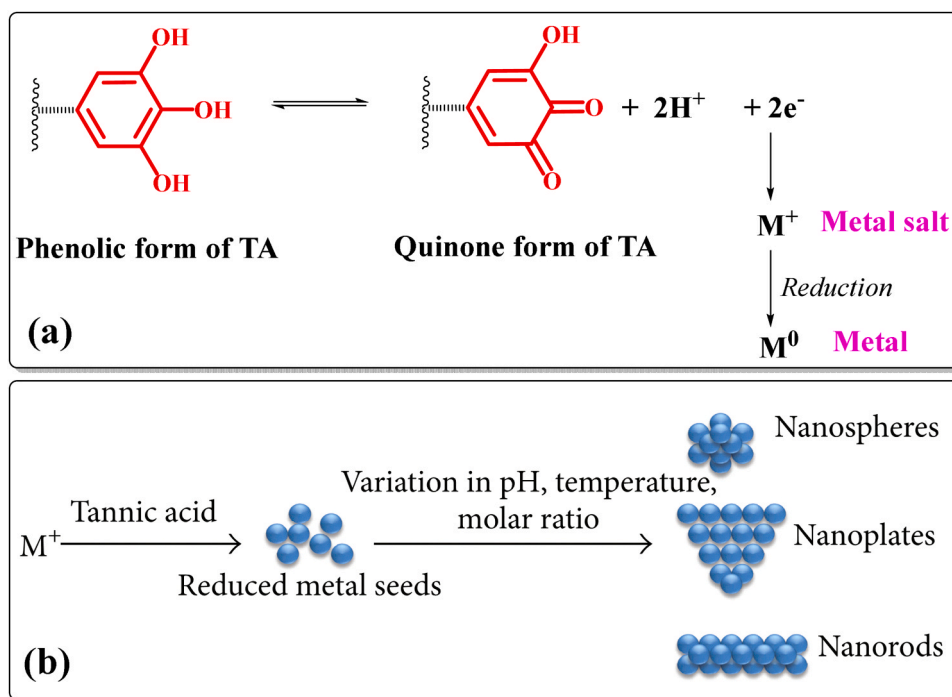


Fig. 3. (a) Redox processes of M^{n+} by TA. (b) preparation of different morphology of metal nanoparticles in presence of TA under different conditions such as pH, temperature.

(a) Reprinted with permission of ref [107]. (b) Reprinted with permission of ref [107].

groups of TA can interact with carboxyl groups of protein via hydrogen bonding at room temperature [95]. Based on this interaction, Du et al. [120] prepared pH and glutathione dual responsive keratin-TA complex nanoparticles for triggering drug release under TME. It was self-assembled with the help of noncovalent interactions including hydrogen bonding, hydrophobic interactions and stabilized via self-crosslinking of thiols [120]. Moreover, DOX was loaded into nanoparticles through various interactions including hydrogen bonding, hydrophobic and electrostatic interaction [121]. The introduction of TA naturally improves the stability of NPs and can decrease the cardiotoxicity of DOX and sensitize tumor cells to DOX, thereby improving its anticancer activity. Nanoparticles containing drugs demonstrated high toxicity against A549 cells, in contrast, they showed low toxicity on normal cells [120]. Compared to normal tissue, higher glutathione level and lower pH value are the characteristic of tumor tissue [122]. Drug-loaded nanoparticles accelerated drug release under mimicked TME due to protonation of keratin at acidic condition and cleavage of disulfide bond at high concentrated glutathione condition [120]. Likewise, a TA-assisted biomineralization approach was used for the encapsulation and intracellular delivery of protein drugs in the TME. This strategy has been designed for high performance of synergistic antitumor therapy due to simple preparation, low toxicity, and controlled release [123].

2.2. TA/ Fe^{3+} complex coating approach for efficient cancer therapy and diagnosis

Metal-polyphenol complexation is of great interest, modifications of TA with metal can improve its function for two main purposes including disease diagnosis and treatment, simultaneously [53,124,125]. This organic-inorganic hybrid material with synergistic properties is very useful for complex biological requirements [126]. The coating of nanoparticles with TA/ Fe^{3+} complex is highly interesting for research and this coating approach adds value to nanoparticles and endows them with a lot of functions such as controlled and smart release in TME and application in phototherapy, chemodynamic therapy and theranostic.

2.2.1. Controlled and smart release

Premature release of drug by providing a large amount of anticancer drugs around healthy tissue can damage them and lead to serious problems such as physical weakness, heart and liver toxicity, decreased immune function, digestive disorder and neurotoxicity [127,128]. To solve this problem, Fabiao et al. modified the surface of PLGA nanoparticles with a TA/ Fe^{3+} complex as a sensitive layer and loaded the nanoparticles with DOX. They used a double emulsion solvent evaporation technique to synthesis of nanoparticles and loaded them with drug and then rapidly coated them with coordinated TA/ Fe^{3+} for the treatment of breast carcinoma (Fig. 5) [108]. The results indicate a better stability of TPLGA (surface-modified nanoparticles) in serum, which is attributed to the enhanced hydrophilicity of nanoparticles due to the hydroxyl groups of TA. This improvement can lead to increased circulation of nanoparticles in the bloodstream and enhance their tumor targeting capability. The drug release results demonstrated that the coated nanoparticles displayed a slower initial burst release rate compared to the uncoated nanoparticles. Furthermore, the coated nanoparticles displayed a higher release amount under acidic condition, indicating the pH-responsive nature of DOX-TPLGA nanoparticles [108]. Actually, due to the conversion of TA/ Fe^{3+} complexes at low pH (Fig. 1b) [108,129], this coated poly TA (pTA) disassemble and allows drug release (Fig. 4).

2.2.2. Photothermal therapy

Phototherapy, consisting of photothermal therapy (PTT) [130,131] and photodynamic therapy (PDT) [132], as a non-invasive strategy, has attracted increasing attention in intensive preclinical and clinical cancer treatment because of its quick recovery, facile spatio-temporal control [133], low cytotoxicity and best precision of near-infrared (NIR) light irradiation [134]. Due to its potential to use much lower energy and minimize any skin toxicity, it can be applied to radiotherapy [135]. With minimal side effects, PPT is still widely used among cancer treatment methods [136]. It is based on the conversion of irradiation energy into heat in the presence of NIR laser irradiation, which can cause apoptosis of tumor cells and thermal ablation of cancer tissues

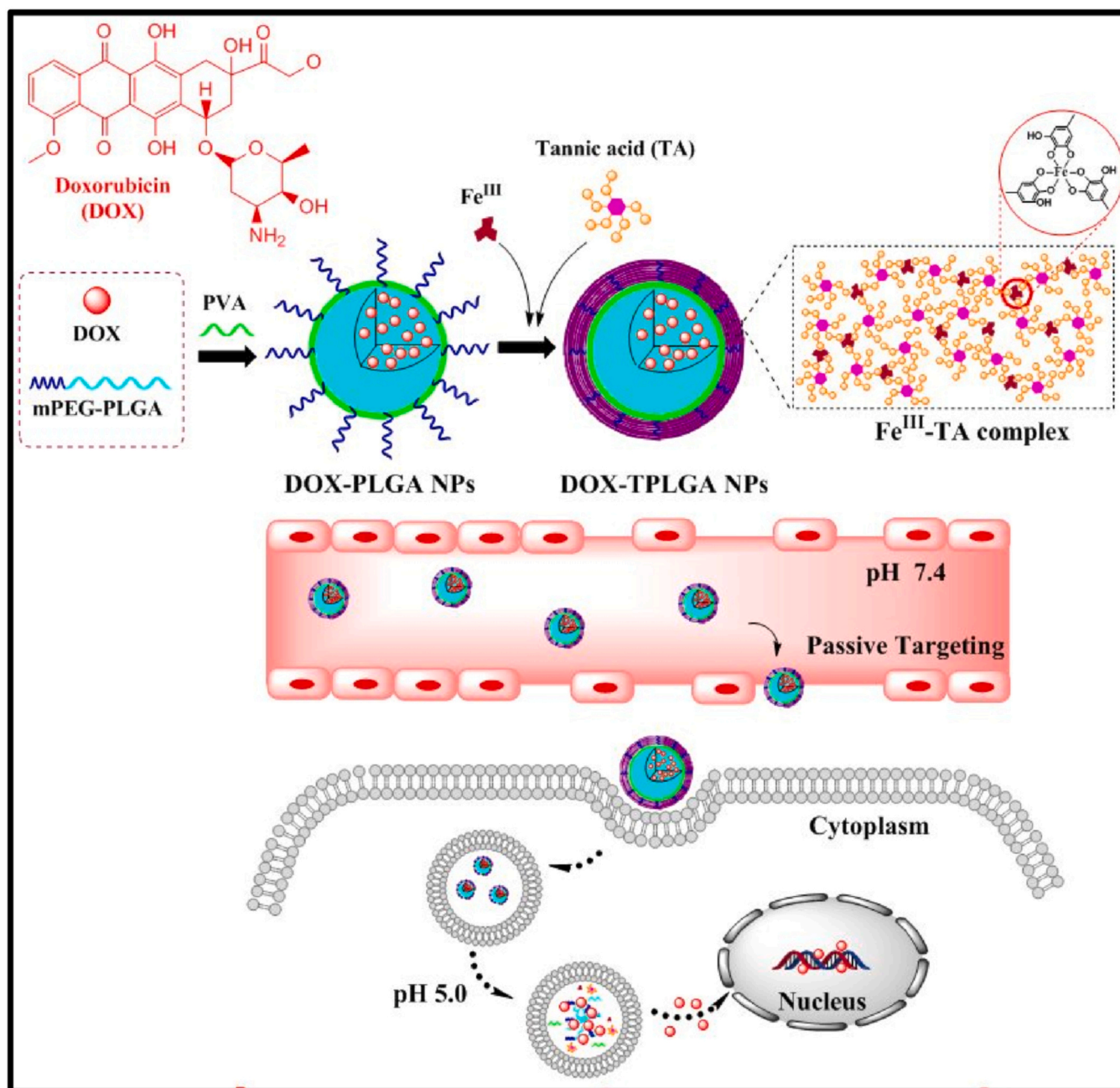


Fig. 4. Schematic mechanism of synthesis and delivery of DOX-TPLGA. Reprinted with permission of ref [108].

[137]. It has been successfully used to combat and suppress the tumor at the primary stage and its spread with minimal side effects in the adjacent normal tissues [138,139]. Another clear, non-intrusive approach with lowest side effects cancer treatment is photodynamic therapy (PDT). It can kill tumor cells by the cytotoxic species $^1\text{O}_2$, which is obtained by converting non-toxic O_2 under illumination [140–143].

PTT can improve the availability of cancer drugs by remodeling the TME [144]. With ligand (TA) to metal (Fe^{3+}) charge transfer, the TA/ Fe^{3+} complex can act as photothermal agent in PTT by converting light (NIR) into heat with high efficiency [145,146]. Xingyue Huang and coworkers coated this complex on PLGA nanoparticles to obtain combined immuno-photothermal therapy for efficient cancer treatment. Their results confirmed that PLGA-pTA could display good photo-stability, high conversion as well as photothermal cytotoxicity against 4T1 cells. The results of animal experiments revealed the

effective inhibition of the growth of primary tumors by PLGA-pTA along with laser irradiation. Moreover, combination with antibodies such as antiPD-L1 leads to more inhibition of tumor growth and metastasis [147]. In a study by Qiao Shi et al., TA/ Fe^{3+} complex coated on mesoporous silica nanoparticles (MSN) and loaded with DOX for cancer treatment. After forming a layer of pTA as an excellent photothermal agent on the surface of nanoparticles, this system can ablate several tumor cells by inducing hyperthermia under NIR laser irradiation. In the acidic environment of tumor cells, pTA is degraded within endosome/lysosome, which leads to the release of chemotherapeutic drug, and consequently, kills the residual tumor cells. More interestingly, in acidic environment, drug release was accelerated due to disassembly of pTA and reduction of drug-carrier interactions (Fig. 5) [148].

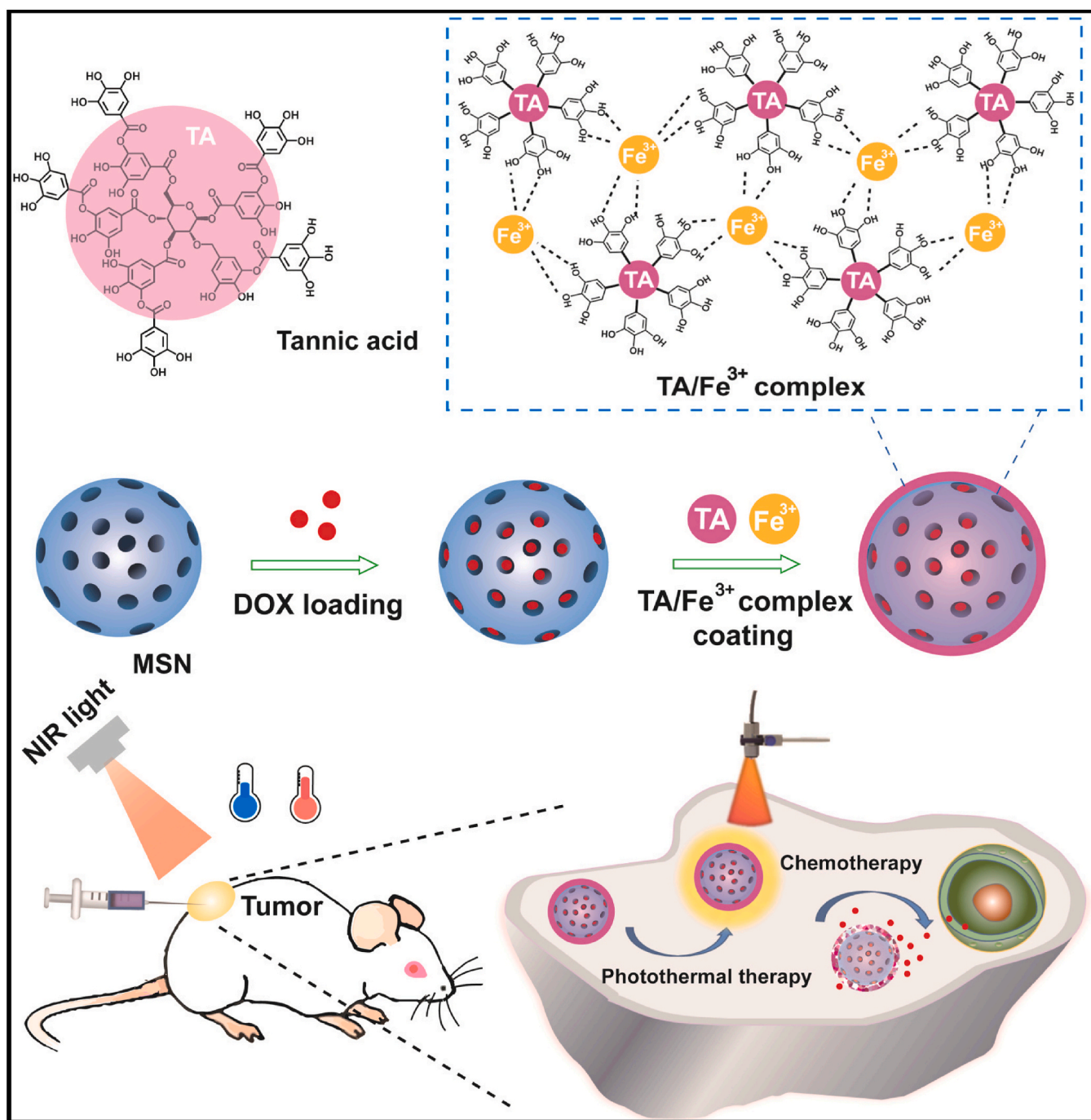


Fig. 5. Combined (chemo-photothermal) therapy by DOX@MSN-pTA. Reprinted with permission of ref [148].

2.2.3. Chemodynamic therapy

Chemodynamic therapy (CDT), as one of the most effective treatment for various cancers with low side effects is basically based on the Fenton and Fenton-like reaction with the generation of highly toxic hydroxyl radicals ($\cdot\text{OH}$) (from endogenous H_2O_2) to cancer cells [149]. H_2O_2 is the most stable and abundant non-radical ROS among all ROSS [150]. CDT suffers from a limited amount of intracellular H_2O_2 . To overcome this problem, self-supplied H_2O_2 was used to (in situ) generate H_2O_2 inside cancer cells [151,152]. This phenomenon was contributed by different substance such as CaO_2 , CuO_2 [153–155], and glucose oxidase (GOD) [156]. By catalyzing the oxidation of glucose, GOD can generate H_2O_2 as the best case to improve H_2O_2 supply. The properties

of GOD, as a natural protein, are restricted by short lifetime, poor stability and immunogenicity [157]. Various nanocarriers have been used to load and deliver GOD into tumor [158,159]. Among them, Metal-organic framework based on polyphenols has been widely used. It was found that polyphenols as reductants can reduce Fe^{3+} to Fe^{2+} and thus increase the generation of $\cdot\text{OH}$ [160]. TA/ Fe^{3+} complexes with good biocompatibility [46] can also catalyze the redox process of H_2O_2 . TA is neutrally inert as reductant while it is highly active in acidic environments [161]. GOD- Fe^{3+} /TA nanocomposites were prepared by the reaction of GOD, Fe^{3+} , and TA in one pot. The generation of H_2O_2 in the tumor region was catalyzed by GOD in the nanocomposite after endocytosis. After that, the conversion of the elevated H_2O_2 to high toxic $\cdot\text{OH}$

radical was performed in the presence of TA/Fe³⁺ composite. This process was interpreted by the redox mechanism. Under the attack of •OH, phenolic groups of TA were oxidized and converted to benzoquinone moieties, which reduced its coordination with Fe³⁺, thereby leading to the release of the Fe³⁺ ions [162].

Du et al., demonstrated that the catalytic activity of TA/Fe³⁺ complex in converting H₂O₂ to •OH is more considerable than corresponding reaction in the free ions (Fe³⁺ or Fe²⁺) [163]. It was also found that GOD-Fe³⁺/TA showed a reasonable cell apoptosis rate about 76.91%. In another study, Fei Chen and coworkers synthesized a new nano-platform in which TA/Fe³⁺ was coated on the surface of CaO₂ nanospherical (CaO₂ @TA-Fe³⁺) to enhance chemodynamic therapy of tumors. As noted, there are two main problems in CDT, which include the limited content of endogenous H₂O₂ in cells and the inefficient reaction between Fe³⁺ and H₂O₂, which lead to restricting efficiency of Fenton reaction and diminishing the effectiveness of tumor treatment. In platform of Chen et al., after the introduction of CaO₂ @TA-Fe³⁺ nanoconjugates into the tumor site, as a result of disintegration of CaO₂ at the tumor site, H₂O₂ can be produced (in tumor cells) and lead to reduction of Fe³⁺ to Fe²⁺, which can solve the problem of insufficient content of H₂O₂ in cancer cells, and the low catalytic efficiency of the Fenton reaction [164]. To improve Fenton reaction and CDT, Peng et al., applied the Fe³⁺/TA complexes with autocatalytic properties and self-supplied H₂O₂ [165]. They designed a dual-responsive core-shell nanoplatform with the ability to carry out as autocatalytic in Fenton reaction and boost chemodynamic therapy (Fig. 6). Coated substance can be disassembled via ATP or acidic condition.

In this process, the reduction of the Fe³⁺ (released from Au@MPN) to Fe²⁺ was carried out by TA due to higher catalytic performance of Fe²⁺ with respect to Fe³⁺. To perform of Fenton reaction in the presence of Fe²⁺, the essential H₂O₂ was prepared by reaction of AuNPs and glucose oxidation.

2.2.4. Combined therapy

Shortcoming of monotherapy such as emergence of drug resistance and incomplete tumor ablation encourage the researchers to combine different treatment strategies [6,166,167]. Combination of different therapy (such as chemotherapy, radiotherapy) with phototherapy can effectively combat metastatic tumor [168]. Because of an acquired and a heterogeneity drug resistance, in cancer therapy, combination therapy is more desirable compared single therapy to enhance therapeutic effects [169]. A combination of PDT/PTT phototherapy has been widely developed [170–175]. To sequentially activation of the PDT photosensitizer and PTT agents [176] in the phototherapy, thus, two different lasers are required.

This leads to affecting the synergistic efficiency of PDT and PTT [177] and length of treatment time. Therefore, to simplify the treatment process and develop the synergistic therapy, it is necessary to design a dual-mode phototherapy platform triggered by a single light irradiation [178,179]. The TA/Fe³⁺ coating approach has been used in some studies to combine PTT with CDT. For example, Liu et al., developed a pH-responsive hybrid nanoparticle (as H₂O₂ self-supply and Fe³⁺ ion self-circulation) to enhanced tumor CDT [180]. CaO₂ @ZIF8 @MPN was prepared by encapsulating CaO₂ in ZIF8 and assembled with TA and

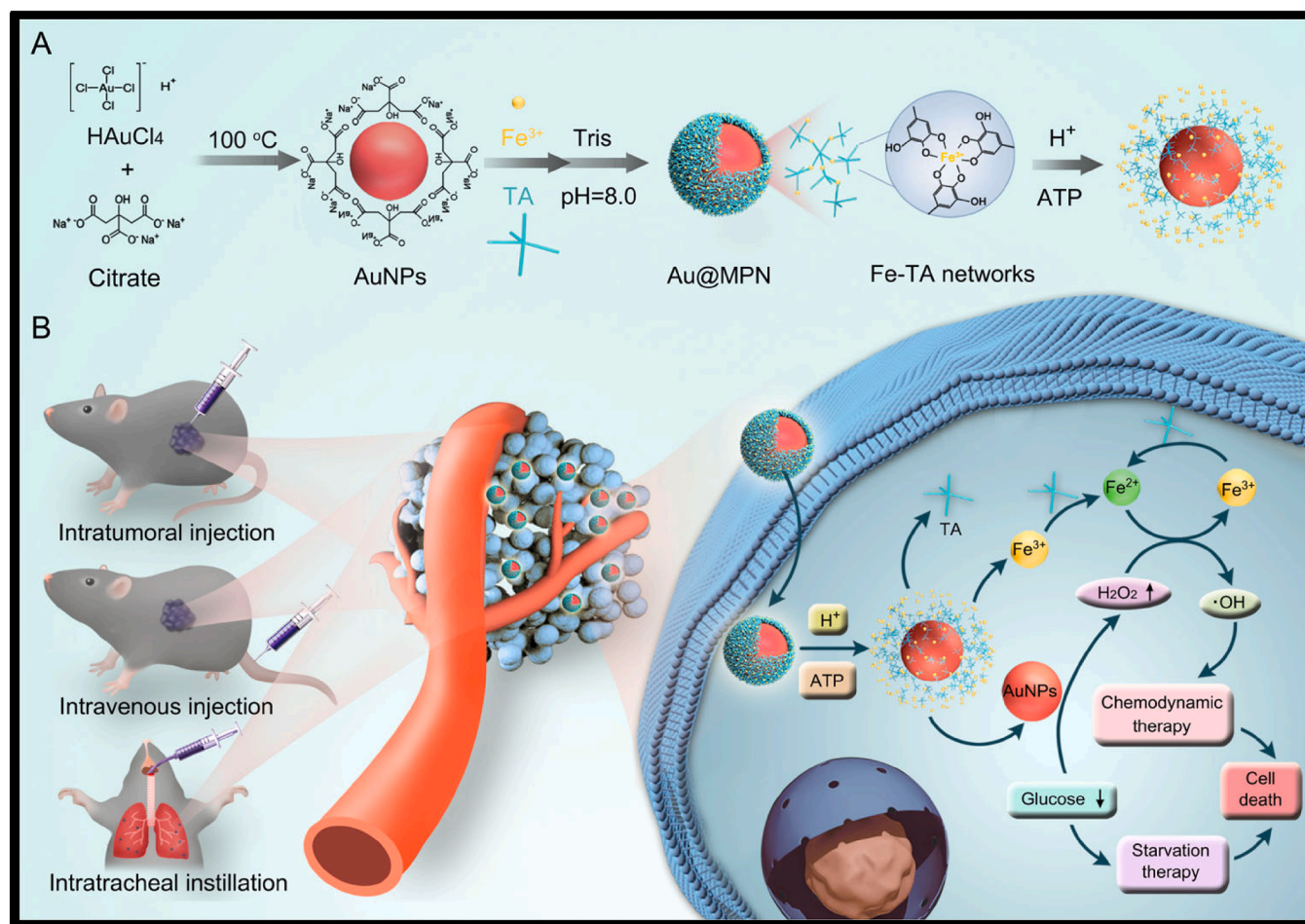


Fig. 6. Schematic enhancement of chemotherapy by Fenton reaction in presence of Au@MPN: A) synthesis of Au@MPN and disassembly process via ATP or acidic condition, B) mechanism of antitumor in presence of Au@MPN. Reprinted with permission of ref [165].

Fe^{3+} (Fig. 7). After internalizing by tumor cells, external MPN was dissociated by lysosomal acidity, leading to the release of TA and Fe^{3+} , reduction of Fe^{3+} to Fe^{2+} by TA, and thus the Fenton reaction.

Also, MPN as PTT agent under NIR irradiation improved the efficiency of Fenton reaction after its own degradation. The role of CaO_2 in the Fenton reaction is the production of highly cytotoxic hydroxyl radical as well as intracellular Ca^{2+} overload, as shown in Fig. 7 by several steps.

In another study, combination of CDT with PDT was achieved via TA/ Fe^{3+} coating approach. Zhu et al., reported the platform based on TA/ Fe^{3+} complex with hollow structure (HFe-TA) and indocyanine green (ICG) as photosensitizer with high anticancer activity for photo/chemodynamic synergistic therapy [181]. The nanocapsule can also manage the Fenton reaction by releasing TA, Fe^{3+} and ICG molecules after degrading in acidic conditions. Besides, it can generate $^1\text{O}_2$ under NIR laser irradiation at 808 nm. Thus, tumor inhibition was achieved by using $^{\bullet}\text{OH}$ and $^1\text{O}_2$ species. The reactions within cancer cells organized by ICG@HFe-TA are carried out by some steps: (1) after cellular uptake, it released the TA, Fe^{3+} ion and indocyanine green under acidic condition (2) reduction of the Fe^{3+} to Fe^{2+} by TA, next, generation of Fe^{3+} , $^1\text{O}_2$ and high cytotoxic $^{\bullet}\text{OH}$ (3) conversion of endogenous and exogenous O_2 into cytotoxic $^1\text{O}_2$ (controlled by 808 nm NIR irradiation) (4) damage to DNA, protein and cell apoptosis.

TA, as an effective anticancer agent as well as a pharmaceutical

excipient has the great potential to be used for clinical applications. It can be designated as a dual-function ingredient in pharmaceuticals, acting as both an active ingredient and a cross-linker in the preparation of versatile formulations. As discussed above, several studies have demonstrated the excellent potential of TA in cancer therapy. For example, a formulation of poly (TA) microparticle was prepared by cross-linking using trimethyl-ol-propane-triglycidyl ether and glycerol diglycidyl ether, which displayed similar activity to the cisplatin against A549 cancer cells [182]. As another good example, Baldwin and co-workers have developed a TA/collagen scaffold that can be used as an injectable adipose tissue regenerative device to replace lipofilling. TA was able to act as a biocompatible cell scaffold for regeneration and reconstruction of breast tissue with prolonged anticancer activity by diffusing into collagen type I beads and stabilized through hydrogen bonding interactions between the amines of the collagen backbone and the hydroxyl groups of TA [183]. But, more studies are needed to demonstrate the efficacy of TA based approaches, the exact mechanisms behind them and their safety when used in the human population.

2.2.5. Theranostic

The decoration of different diagnostic imaging on therapeutic delivery vehicles makes them a proper system for biomedical field, leading to superior information on delivery kinetic, trafficking pathway and therapeutic efficiency to treat the main tumor and any metastatic tumor

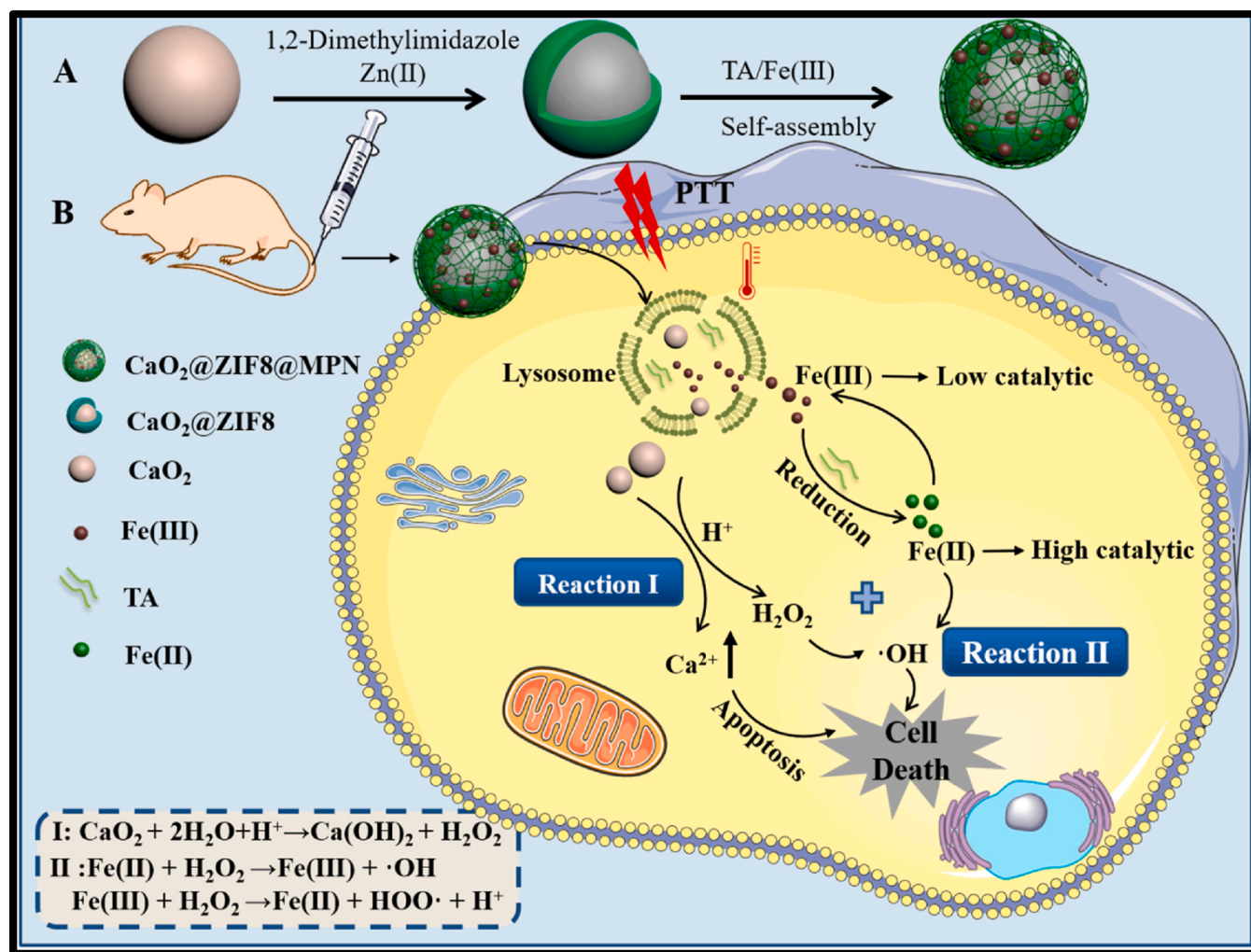


Fig. 7. Schematic presentation and application of $\text{CaO}_2@ZIF8@MPN$ as pH-responsive and H_2O_2 self-supply and Fe^{3+} ion self-circulation for enhanced tumor CDT. A) synthesis, B) chemical behavior under different mechanisms. Reprinted with permission of ref [180].

[184,185]. Owing to its high surface-to-volume ratios, nanoparticles could be functionalized with diagnostic and therapeutic agents to be used in the identification, diagnosis and treatment of tumor. Natural polyphenolic based nanoparticles are widely used as theranostics agents [186–188]. Among them, Fe³⁺/polyphenol complexes (such as TA/Fe³⁺ complex) coated nanoparticles with suitable properties (low toxicity, paramagnetic, active in magnetic resonance imaging (MRI) are mostly used for diagnosis (MR imaging) and treatment [189–195]. MRI application and improvement of liver clearance for TA/Fe³⁺ nanoparticle was evaluated by Phatruengdet and et al. [196]. Pharmacokinetic results indicated that TA/Fe³⁺ was observed in blood circulation and distributed to the liver. The maximum increase in MRI signal occurred after

30 min of injection and gradually decreased. In another study, Gayong Shim et al., coated the TA/Fe³⁺ coordination complex on boron nitride nanosheets (BNS) to analyze magnetic field and NIR responsiveness. Results indicated that the presence of the TA/Fe³⁺ complex leads to enhancement of magnetic field relaxivity and NIR-responsiveness. The in vitro results indicated that the presence of the TA/Fe³⁺ complex in BNS (TA/Fe³⁺/BNS) improved the T1-weighted magnetic resonance contrast in KB tumor cells compared to free substances. Accumulation of intravenously administered TA/Fe³⁺/BNS at the tumor site was observed in the in vivo MRI technique. In both tissues (normal and tumor), the intensity ratios of T1-weight MR signal increased with time. As shown in thermal imaging, mice treated with TA/Fe³⁺/BNS exhibited

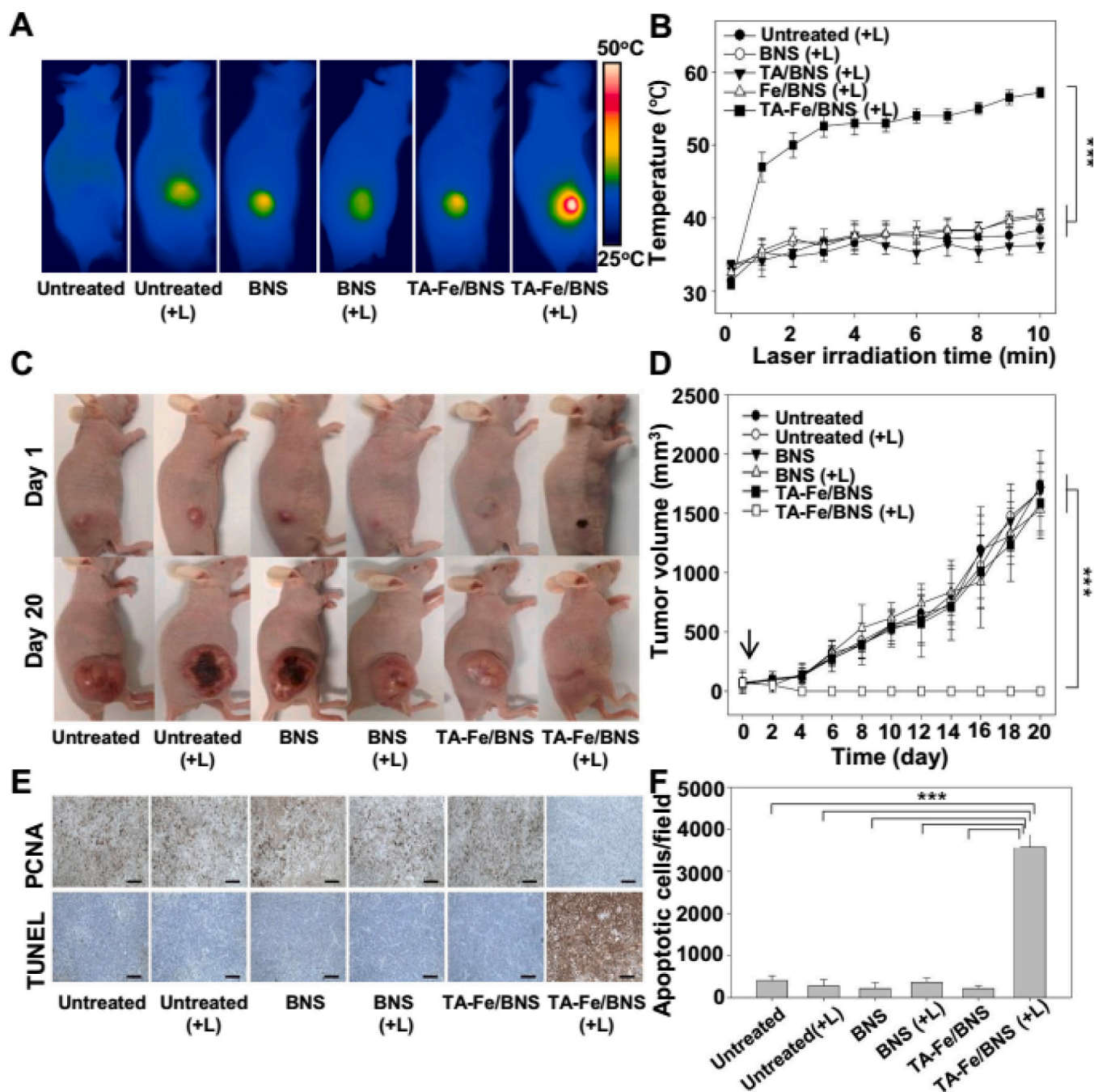


Fig. 8. In vivo results of photothermal properties of TA/Fe³⁺/BNS. (A) Thermal images were achieved after 10 min under NIR-irradiation, (B) quantification of images for all groups (n = 5), (C) appearance of tumor from 1 to 20 day, (D) measured volume in different days, (E) evaluation of tumor tissues by immunostaining for (top) and conducted assay (bottom). Reprinted with permission of ref [197].

better antitumor effect in association with increased temperature under irradiation of NIR. Immunohistochemistry results also demonstrating that the results are related with an increase in apoptotic cells along with a decrease in cell proliferation (Fig. 8). Based on MRI information, tumor ablation was reached through application of focused laser irradiation, which referred to ability of TA/Fe³⁺/BNS for MRI theranostics [197].

Qiao et al. designed a strategy to prepare TA/Fe³⁺ complex for biomimetic engineering-mediated photothermal ability enhancement in the TME to kill tumors. In this study, protoporphyrin-encapsulated TA and Fe³⁺ system were coated with cancer cell membranes to achieve tumor imaging and tumor-specific photothermal performance for efficient treatment and diagnosis of cancer [198].

2.3. Utilization of TA for preparing anticancer hydrogels

Hydrogel-based therapy has been widely used for cancer therapy application due to its biocompatibility, good malleability, high drug loading, controllability-prolonged drug release and specific stimuli-sensitivity [199,200]. Hydrogels can act as carrier for tumor treatment and scaffold for tissue repair [201,202]. As just noted, TA has superior multiple interactions, including hydrogen bonding, hydrophobic, ionic and coordination interactions, so it is highly desirable for hydrogel formation [39,203,204]. For example, multifunctional hydrogel have been developed via multiple hydrogen bonding interactions between TA and gelatin reported by Ahmadian and coworkers [205]. Likewise, Fan and coworker developed an efficient gelation binder based on TA to form hydrogel with water-soluble polymers [206]. The presence of proper functional groups and various interactions, described as cross-linking agents, leads naturally to formation of supramolecular hydrogel.

TA has been utilized for the preparation of anticancer hydrogels in several studies. Oksana A. Mayorova and coworkers prepared a biocompatible hydrogel using whey protein isolate (WPI) and TA as crosslinking agent. Hydrogels demonstrated pH dependent swelling behavior. The results demonstrated that the addition of TA can increase the cytotoxicity of whey protein WPI-TA hydrogels against Hep-2 human laryngeal squamous carcinoma cell lines (Hep-2 cells). It also indicated the potential of this hydrogel for cancer therapy [207]. Due to the ability of intratumorally injection capability which can eliminate the need for surgical procedures, injectable hydrogels with in situ formation ability provide a much less invasive means of treating cancer patients. Injectable hydrogels could be simply obtained for intratumoral injection and loaded with anticancer agent, which can minimize drug accumulation in other organs by direct delivery and accumulating the anticancer agents at tumor sites [208]. Furthermore, photoactive injectable hydrogels can be applied for local cancer treatment by combined therapy (PTT-CDT) [209].

Zhuojun Huang and coworkers developed an in situ forming injectable hydrogel using polyethylene glycol (PEG), boronic acid (as backbone), plant polyphenol (as linkers) such as TA, ellagic acid (EA), epigallocatechin gallate (EGCG), etc. with the potential to treat cancer [210]. The results of the rheological frequency sweep test showed the mechanical stiffness of EGCG and TA-linked hydrogels, because a dynamic covalent bond was formed between the polyphenol and the boronic acid. It was found that polyphenol acts as both a cross-linker and a therapeutic agent. By injecting the polymer precursor solution and polyphenol and allowing the formation of boronate ester cross-linking after neutralization at physiological pH, the gel can be formed. [211].

Yuato Ren and et al. applied oxaliplatin (OXA) as third generation of platinum-based chemotherapy agent. OXA commonly demonstrates adverse effect such as vomiting, nausea and peripheral neuropathy. TA with multiple biological activities (including anti-proliferation, antioxidant, and anti-carcinogenic effects) was used to reduce the adverse cytotoxic effects of OXA on normal cells. Since intraperitoneal chemotherapy creates a high concentration of the drug near the target tumor site and reduces severe system toxicity. Therefore, a thermosensitive

hydrogel exhibiting sol-gel transition was used as a delivery carrier for these chemotherapeutic drugs. In addition to delivering, prolonging the release can be achieved around the peritoneal metastatic tumor. They loaded OXA and TA into polylactic acid (PLAR) nanoparticles (OXA/TA/NPs) and then loaded it after gelation into a thermosensitive hydrogel, and OXA/TA/NPs-hydrogel composite was developed. Degradation of thermosensitive hydrogel and decomposition of OXA-TA nanoparticles leads to sustaining the drug release and prolonging effective drug concentration near the target tumor locally and could also diminish the adverse effect of chemotherapy drugs. As shown, the abdominal cavity taken on day 20 had significantly lower number of tumor nodules and tumor nodule size in the OXA/TA NPs-H treated group compared to other groups. Furthermore, the mean values of volume of ascites, the number and weight of tumor nodules in OXA/TA NPs-H treated group was significantly lower compared with other groups including the control group, blank nanoparticles hydrogel group, free OXA group, and OXA NPs group (Fig. 9) [212].

Xiao Zhu and et al. prepared a biocompatible injectable hydrogel with notable shear-thinning behavior by reaction between TA and 4-arm-PEG-SH by chemical crosslinking and multiple physical interactions. With inherent NIR absorption, it could be employed for ablation of tumor cells, and increasing the cellular uptake of chemotherapeutics drugs. The results (in vitro and in vivo) demonstrated a synergistic combinational photothermal-chemotherapy therapeutic effect on tumor growth. Hence, an NIR-responsive and injectable hydrogel based on TA/Fe³⁺ introduced for synergistic photothermal-chemotherapy [210].

3. Conclusion

Chemotherapy is a common cancer treatment that has been employed against different types of cancer. This approach has many challenges including drug resistance as well as, toxicity to normal cells. To overcome these drawbacks and/or improve the efficacy of chemotherapy such as decreasing its toxicity, several studies have attempted to link creativity to novel therapy methods. Numerous of nanotechnology techniques in biomedical research are designed. Among the various types of materials, TA as a natural polyphenol, is arguably the most important, due to high biological activities such as anticancer. TA was found to be potent chemo sensitizer by overcoming multidrug resistance, as well as, it can decrease the toxicity of chemotherapy. Therefore, TA can increase the effectiveness of chemotherapy drugs as well as, decrease the toxicity of these anticancer agents such as DOX through numerous mechanisms including antiinflammatory, antioxidant activities and etc. Moreover, unique structure of TA made it a proper candidate to be used as crosslinker for preparation of different anticancer nanoparticles and hydrogels. Furthermore, usage of TA/Fe³⁺ as coating agent for the preparation of nanoparticles endows them with additional functions such as photothermal conversion, chemodynamic and theranostic capabilities. Although, admirable efforts had been made by different scientists around the world, but more studies can be done for developing injectable TA based anticancer hydrogels which can be intratumorally injected. Specially, coordination interaction between TA and metals can be employed for preparation of anticancer hydrogels, which these interaction, in addition to acting as crosslinking sites can endow the final hydrogels with additional functions such as photothermal and theranostic abilities for efficient ablation of tumor cells via synergistic mechanisms. More to this, future studies could focus on in vivo efficacy, toxicity and clinical application of this novel field of research. In addition to TA, our nature is full of other natural based materials with potential applications in cancer therapy which can be considered by researchers. Hopefully, this review article provides a promising prospective for future studies in the field of cancer therapy and diagnosis.

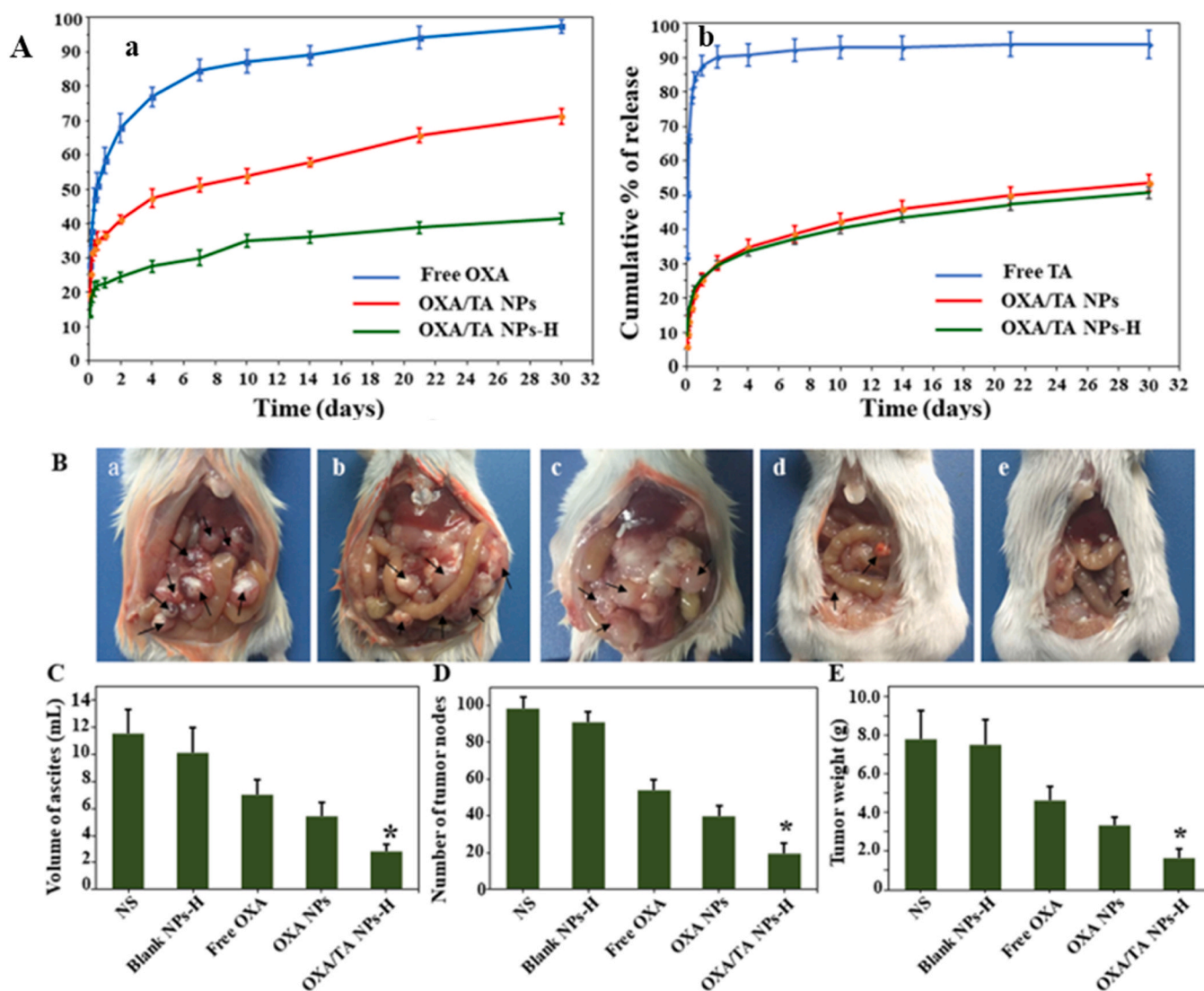


Fig. 9. (A) In vitro drug release and cell cytotoxicity. (a) Release of OXA in different system, (b) release of TA in different system (OXA/TA, OXA/TA/NPs). (B) photographs of tumor for (a) NS; (b) blank NPs-H; (c) OXA; (d) OXA NPs; (e) OXA/TA NPs-H. (C) Volume of ascites of mice; (D) number of tumor; (E) weight of tumor. Reprinted with permission of ref [212].

Ethics approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Motaleb Ghasemian was the major contributor in writing the manuscript. Fahimeh Kazeminava Supported with the initial draft, review, and editing of the manuscript. Ashkan Naseri and Soheila Mohebzadeh were responsible for part of the literature search. Mahmoud Abbaszadeh created the images. Hossein Samadi Kafil and Zainab Ahmadian were responsible for the data and reviewing the article. All authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author’s contributions

The study was fully designed, analyzed and written by the authors. The author(s) read and approved the final manuscript.

Declarations

Consent for publication

Not applicable.

Competing interests

There are no conflicts to declare.

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